DETAILED ACTION

This office action is in response to applicant's reply filed on April 11, 2008.

Status of Claims

Amendment of claims 1, 4-7, 10-11, 14-17 and 23 is acknowledged.

Claims 1-7, 10-18 and 23 are currently pending and are the subject of this office action.

Claims 1-7, 10-18 and 23 are currently under examination.

Priority

The present application claims priority to International Application No. PCT/EP04/52725 filed 10/29/2004 and to foreign application No. EP20030024844 filed 10/31/2003.

Response to Arguments

This is in response to applicant's arguments, filed on April 11, 2008.

Claims rejected under 35 USC 112, first paragraph (written description).

Due to applicant's amendment of claims 1-7, 10-18 and 23, the written description rejection is now moot.

Rejection under 35 USC 112, first paragraph (written description) is withdrawn.

Claims rejected under 35 USC 112, first paragraph (scope of enablement).

Due to applicant's amendment of claims 1-7 and 11-15, the scope of enablement rejection is now moot.

Rejection under 35 USC 112, first paragraph (scope of enablement) is withdrawn.

Claims (1-2 and 10) rejected under 35 USC 102 (b)

Applicant's arguments have been fully considered and are persuasive. Therefore the rejection is withdrawn. However, upon further consideration, a new ground of rejection is made.

A new USC 103 (a) rejection is applied.

Claims (10) rejected under 35 USC 102 (b)

Applicant's arguments have been fully considered and are persuasive. Although Takafumi et. al. (EP 0908182, cited in prior Office Action and cited by applicant) teach most of the limitations of claim 10 (e.g. a pharmaceutical composition comprising tetrahydrobiopterin (BH4) or any of its derivatives), they do not teach a customary secondary packaging, and optionally a package insert. Applicant should be aware that the statement in claim 10: "suitable for treatment of COPD" is considered an intended use and not a limitation.

Therefore the rejection is withdrawn. However, upon further consideration, a new ground of rejection is made.

A new USC 103 (a) rejection is applied.

Claims (23) rejected under 35 USC 102 (b).

Applicant's arguments have been fully considered and are persuasive. Therefore the rejection is withdrawn. However, upon further consideration, a new ground of rejection is made.

A new USC 103 (a) rejection is applied.

Claims (10, 16-18 and 23) rejected under 35 USC 102 (a)

Applicant's arguments regarding claims 10, 18 and 23 have been fully considered and are persuasive. Although Rabelnik et. al. (US 6,544,994, cited in prior office action) teaches most of the limitations of claims 10, 18 and 23 (e.g. a pharmaceutical composition comprising tetrahydrobiopterin (BH4) and arginine), they do not recite some limitations like: a customary secondary packaging (claim 10), or a pharmaceutically acceptable carrier (claim 18) or instructions for use of the pharmaceutical agents (claim 23).

Therefore the rejection is withdrawn. However, upon further consideration, a new ground of rejection is made.

A new USC 103 (a) rejection is applied for claims 10, 18, and 23

Applicant's arguments regarding claims 16-17 have been fully considered and are not persuasive.

Applicant argues that Rabelnik et. al. fail to teach a pharmaceutical preparation which is suitable for treating respiratory diseases, much less the specific disease COPD. However, claims 16 and 17 do not mention what these preparations are suitable for, but even if they were, it would have been considered an intended use and not a limitation. Thus, Rabelnik et. al. clearly anticipate claims 16 and 17.

Rejection under 35 USC 102 (a) is maintained for claims 16 and 17.

Claims (1-7 and 11-15) rejected under 35 USC 103 (a)

Applicant's arguments have been fully considered and are persuasive. Therefore the rejection is withdrawn. However, upon further consideration, a new ground of rejection is made.

A new USC 103 (a) rejection is applied.

Claims (3-4 and 6) rejected under 35 USC 103 (a)

Applicant's arguments have been fully considered and are persuasive. Therefore the rejection is withdrawn. However, upon further consideration, a new ground of rejection is made.

A new USC 103 (a) rejection is applied.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 102

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 16-17 are rejected under 35 U.S.C. 102(a) as being anticipated by Rabelnik et. al. (US Patent No. 6,544,994, cited in prior Office Action).

Instant claims 16-17 recite a preparation or a pharmaceutical composition, comprising: BH4 or a derivative thereof and arginine or a derivative thereof. For instant claims 16-17, Rabelnik et. al. teach: a pharmaceutical composition comprising at least: BH4 and arginine (see claim 1).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over applicants own admission and Manning (US 2004/0087653) as evidenced by Schmid et. al. (WO2001/56551, cited in previous office action and cited by applicant).

Claims 1-4 and 6 recite a method for treating a respiratory disease, or specifically COPD, in a patient comprising administering a therapeutically effective amount of a compound selected from the group consisting of (6R)-L-erythro-5,6,7,8-tetrahydrobiopterin (BH4) and other derivatives of BH4 listed in claims 1, 4 and 6.

For claims 1-4 and 6, applicant admits that BH4 is an essential co-factor of Nitric Oxide Synthases (NOS) as it influences the rate of Nitric Oxide (NO) vs. superoxide production by NOS, by increasing the amount of NO (see page 1, under Prior Art). For claims 1-4 and 6 Manning teaches that COPD and asthma (respiratory diseases) can be treated by modulating the activity of NOS (increasing or decreasing) (see page 2, left column, paragraph [0016] and thus decreasing or increasing the amount of endogenous NO.

At the time of the invention it would have been *prima facie* obvious for a person of ordinary skill in the art to combine applicants own admission (BH4 increases the level of endogenous NO) and the teaching of Manning (Increase of endogenous NO could be beneficial for treating COPD or any other respiratory disease), with the motivation of providing a better treatment for COPD or any respiratory disease with BH4, thus resulting in the practice of claims 1-4 and 6 with a reasonable expectation of success as evidenced by Schmidt et. al. Schmidt et. al. teach a method useful for preventing or reversing several respiratory diseases like: acute or chronic pulmonary vasoconstriction (COPD is a respiratory disease associated with pulmonary vasoconstriction), comprising the use of BH4 (see abstract and page 12 last paragraph and page 13, first paragraph). Although Schmidt et. al. use less than therapeutic levels of BH4 (see page 8, last paragraph), it would have been obvious for the skilled in the art to adjust the levels of BH4 when used as a single agent in the treatment of COPD or any other respiratory disease.

Claims 5, 7, 11-15 rejected under 35 U.S.C. 103(a) as being unpatentable over applicants own admission and Manning (US 2004/0087653) as evidenced by Schmidt et. al. (WO2001/56551, cited in previous office action and cited by applicant) as applied to claims 1-4 and 6 above, and further in view of Juturu et. al. (US 2004/0097467) or Rabelnik et. al. (US 6,544,994, cited in prior Office Action).

Claim 5 recites the same limitations as claim 1, further comprising a compound selected from the group consisting of arginine, L-arginine hydrochloride, etc (see claim 5 for a full list).

Applicants own admission and Manning, as evidenced by Schmidt et. al. teach all the limitations of claim 5, except for further using arginine or any of the other compounds listed in claim 5.

However, Juturu et. al. teach a method of treating COPD with arginine silicate inositol complex (a source of arginine, see claims 44 and 45 and paragraph [0042]).

Also, Rabelnik et. al. teach that arginine is the precursor of endogenous nitric oxide (NO) and as a consequence it increases the production of NO (see column 2, lines 3-18), and since Manning teaches that an increase of endogenous NO can be beneficial for the treatment of COPD or any other respiratory disease it would have been obvious to treat COPD or any other respiratory disease with arginine.

At the time of the invention it would have been *prima facie* obvious for a person of ordinary skill in the art to treat COPD or any respiratory disease combining two compositions (BH4 and arginine) each of which is taught by the prior art to be useful for

the same purpose, in order to form a third composition to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in the prior art (see MPEP 2144.06). *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) claims to a process preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be *prima facie* obvious. All this would result in the practice of claim 5 with a reasonable expectation of success.

Claim 7 recites the same limitations as claim 6, further comprising a compound selected from the group consisting of arginine, L-arginine hydrochloride, etc (see claim 7 for a full list).

Applicants own admission and Manning, as evidenced by Schmidt et. al. teach all the limitations of claim 7, except for further using arginine or any of the other compounds listed in claim 7.

However, Juturu et. al. teach a method of treating COPD with arginine silicate inositol complex (a source of arginine, see claims 44 and 45 and paragraph [0042]).

Also, Rabelnik et. al. teach that arginine is the precursor of endogenous nitric oxide (NO) and as a consequence it increases the production of NO (see column 2, lines 3-18), and since Manning teaches that an increase of endogenous NO can be beneficial for the treatment of COPD or any other respiratory disease it would have been obvious to treat COPD or any other respiratory disease with arginine.

At the time of the invention it would have been *prima facie* obvious for a person of ordinary skill in the art to treat COPD or any respiratory disease combining two compositions (BH4 and arginine) each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in the prior art (see MPEP 2144.06). *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) claims to a process preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be *prima facie* obvious. All this would result in the practice of claim 7 with a reasonable expectation of success.

Claim 11 recites the same limitations as claim 1, further comprising a compound selected from the group consisting of arginine, L-arginine hydrochloride, etc (see claim 11 for a full list). Claims 12-15 recite the same limitations as claim 11, wherein the respiratory disease is COPD.

Applicants own admission and Manning, as evidenced by Schmidt et. al. teach all the limitations of claim 11-15, except for further using arginine or any of the other compounds listed in claim 11 and 15.

However, Juturu et. al. teaches a method of treating COPD with arginine silicate inositol complex (a source of arginine, see claims 44 and 45 and paragraph [0042]).

Also, Rabelnik et. al. teach that arginine is the precursor of endogenous nitric oxide (NO) and as a consequence it increases the production of NO (see column 2,

lines 3-18), and since Manning teaches that an increase of endogenous NO can be beneficial for the treatment of COPD or any other respiratory disease it would have been obvious to treat COPD or any other respiratory disease with arginine.

At the time of the invention it would have been *prima facie* obvious for a person of ordinary skill in the art to treat COPD or any respiratory disease combining two compositions (BH4 and arginine) each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in the prior art (see MPEP 2144.06). *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) claims to a process preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be *prima facie* obvious. All this would result in the practice of claims 11-15 with a reasonable expectation of success.

Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Takafumi et. al. al. (Publication No. EP0908182, cited in previous Office action and cited by the applicant).

Claim 10 recites a commercial product comprising: a customary secondary packaging, a primary packaging comprising a pharmaceutical preparation of a compound selected from the group consisting of BH4 or any of the BH4 derivatives listed in claim 10, and optionally a package insert.

For claim 10, Takafumi et. al. teach a pharmaceutical composition comprising BH4 or some of its derivatives (see paragraphs [0024] and [0028]-[0035], and claim 1). Takafumi does not teach a customary secondary packaging or packages insert, but these would have been obvious to the skilled in the art.

The statement in claim 10: "for treatment of COPD in patients in need thereof" is considered an intended use and does not add any new limitation to the claim. Catalina Mktg. Int'l, Inc. V. Coolsavings.com, Inc., 289 F.3d 801, 808, 62 USPQ2d 1781, 1785 (fed. Cir. 2002). "The recitation of a new intended use for an old product does not make a claim to that old product patentable." In re Schreiber, 44 USPQ2d 1429 (Fed. Cir. 1997).

At the time of the invention, it would have been prima facie obvious to a person of ordinary skill in the art to combine the teachings of Takafumi et. al. (a pharmaceutical composition comprising BH4 or any of its derivatives) and make a commercial product further comprising a customary secondary packaging and a package insert, thus resulting in the practice of claim 10 with a reasonable expectation of success.

Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rabelnik et. al. (US Patent No. 6,544,994, cited in prior Office Action).

Claim 18 recites the same limitations as claim 17, wherein the pharmaceutical composition further comprises a pharmaceutically acceptable carrier.

Rabelnik et. al. teach all the limitations of claim 18, except for the pharmaceutically acceptable carrier. However, adding a pharmaceutically acceptable carrier will be obvious to the skilled in the art.

Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rabelnik et. al. (US Patent No. 6,544,994, cited in prior Office Action).

Claim 23 recites a trade package comprising as pharmaceutical agent a compound selected from the group consisting of BH4 or any of its derivatives listed in claim 23 and/or a compound selected from the group consisting of arginine and any of its derivatives listed in claim 23, together with instructions for the use of the pharmaceutical agents in combination for simultaneous, separate or sequential administration for the treatment of respiratory diseases.

For claim 23, Rabelnik et. al. teach: a pharmaceutical composition comprising at least: BH4 and arginine (see claim 1). Rabelnik et. al. do not teach a trade package with instructions for the use of the pharmaceutical agents. However, adding instructions to a trade package would have been obvious to the skilled in the art.

The statement in claim 23: “for the treatment of respiratory diseases” is considered an intended use and does not add any new limitation to the claim. Catalina Mktg. Int’l, Inc. V. Coolsavings.com, Inc., 289 F.3d 801, 808, 62 USPQ2d 1781, 1785 (fed. Cir. 2002). “The recitation of a new intended use for an old product does not make a claim to that old product patentable.” In re Schreiber, 44 USPQ2d 1429 (Fed. Cir. 1997).

At the time of the invention, it would have been prima facie obvious to a person of ordinary skill in the art to combine the teachings of Rabelnik et. al. (a pharmaceutical composition comprising BH4 or any of its derivatives) and make a trade package further comprising a instructions for the use of the pharmaceutical agents, thus resulting in the practice of claim 23 with a reasonable expectation of success.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCOS SZNAIDMAN whose telephone number is (571)270-3498. The examiner can normally be reached on Monday through Thursday 8 AM to 6 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael P. Woodward can be reached on 571 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic

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May 28, 2008

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